STIC-ILL

Vol. No 10/14

From: Gambel, Phillip
Sent: Tuesday, October 14, 2003 3:35 PM
To: STIC-ILL
Subject: thyroiditis and oophoritis

407956

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please provide the following references to

phillip gambel
art unit 1644
308-3997

stull, S.J., et la. (1988). Prevention and reversal of experimental autoimmune thyroiditis (EAT) in mice by administration of anti-L3T4 monoclonal antibody at different stages of disease development. Cell. Immunol. 117:188-198.

9/7/31 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07143542 92005735 PMID: 1680568
Suppression in murine experimental autoimmune thyroiditis: in vivo inhibition of CD4+ T cell-mediated resistance by a nondepleting rat CD4 monoclonal antibody.
Nabozny G H; Cobbold S P; Waldmann H; Kong Y C
Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan.
Cellular immunology (UNITED STATES) Nov 1991, 138 (1) p185-96, ISSN 0008-8749 Journal Code: 1246405
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Genetically susceptible mice become resistant to experimental autoimmune thyroiditis (EAT) induction with mouse thyroglobulin (MTg) and lipopolysaccharide after pretreatment with deaggregated MTg (dMTg). Recent work showed this suppression to be mediated by CD4+ suppressor T cells (Ts). To study Ts action in vivo, we used a rat IgG2a monoclonal antibody (mAb), YTS 177.9, which modulates CD4 antigen in vivo without depleting CD4+ cells. Initial studies showed that after two 1-mg doses of mAb 7 days apart, extensive CD4 antigen modulation of peripheral blood leukocytes occurred within 4 days. Mice given CD4 mAb 24 hr before dMTg (2 doses, 7 days apart) were resistant to EAT induction when immunized with MTg and LPS 20 days later. Also, anti-rat IgG2a titers were reduced following challenge with heat-aggregated rat IgG2a compared to controls. Subsequent analysis of serum in CD4 mAb-treated animals revealed that mAb was present in the circulation for 14 days. Moreover, mice given CD4 mAb and dMTg, then challenged after only 10 days, when CD4 mAb was still circulating, developed a significantly higher incidence of thyroid damage than controls. These findings suggest that modulation of CD4 antigen does not interfere with Ts activation, but the presence of CD4 mAb, at the time of autoantigenic challenge, can interfere with tolerance to EAT induction. Thus, the direct relationship between the presence of CD4 mAb and inhibition of EAT suppression implicates a role for CD4 molecules in the mediation of suppression.
Record Date Created: 19911115
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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L11	(oophoritis) same (treat$ or inhibit$ or suppress$)	80	L11
L10	(oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$)	48	L10
L9	(thyroiditis) and (oophoritis) and (treat$ or inhibit$ or suppress$) and (antibod$)	63	L9
L8	(thyroiditis) and (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	22	L8
L7	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	12	L7
DB=USPT; PLUR=YES; OP=ADJ			
L6	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	4	L6
L5	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$)same ('t-cell$' or 't-lymphocyte$')	3	L5
L4	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) and (thyroiditis or oophoritis)	158	L4
DB=USPT,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
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DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
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L1	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) and (thyroiditis or oophoritis)	655	L1

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L10	(oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$)	48	L10
L9	(thyroiditis) and (oophoritis) and (treat$ or inhibit$ or suppress$) and (antibod$)	63	L9
L8	(thyroiditis) and (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	22	L8
L7	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	12	L7
DB=USPT; PLUR=YES; OP=ADJ			
L6	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$) and ('t-cell$' or 't-lymphocyte$')	4	L6
L5	(thyroiditis) same (oophoritis) same (treat$ or inhibit$ or suppress$) and (antibod$)same ('t-cell$' or 't-lymphocyte$')	3	L5
L4	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) and (thyroiditis or oophoritis)	158	L4
DB=USPT,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L3	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) and (thyroiditis or oophoritis)	174	L3
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L2	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) same (thyroiditis or oophoritis)	90	L2
L1	(gp39 or cd40 or cd40L or cd40 adj ligand or 5c8) and (thyroiditis or oophoritis)	655	L1

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((OOPHORITIS) SAME (TREAT$ OR INHIBIT$ OR SUPPRESS$) AND (ANTIBOD$)).USPT,PGPB,JPAB,EPAB,DWPI.	48

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DATE: Tuesday, October 14, 2003 Printable Copy Create Case

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L4: Entry 18 of 158 File: USPT Jul 15, 2003

DOCUMENT-IDENTIFIER: US 6593112 B1
TITLE: Polynucleotides encoding fibroblast growth factor 15

Detailed Description Text (385):
Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Detailed Description Text (417):
Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by FGF-15 polynucleotides or polypeptides, as well as antagonists or agonists of FGF-15, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, FGF-15 polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Detailed Description Text (419):
Diseases associated with increased apoptosis that could be treated or detected by FGF-15 polynucleotides or polypeptides, as well as agonists or antagonists of FGF-15, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Detailed Description Text (668):
NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

Detailed Description Text (746):

In one embodiment, the Therapeutics of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-IBBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

Detailed Description Text (757):
In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

Detailed Description Text (824):
One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

Detailed Description Text (837):
Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-.alpha., causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC.gamma.RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

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L4: Entry 142 of 158 File: USPT Jul 29, 1997

DOCUMENT-IDENTIFIER: US 5652243 A
TITLE: Methods of using enantiomerically pure hydroxylated xanthine compounds

Detailed Description Text (32):
The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as IL-1 antagonists. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106, Jan. 14, 1993) described the role of IL-1 as "an important rapid and direct determinant of disease." "in septic shock, for example, IL-1 acts directly on the blood vessels to induce vasodilatation through the rapid production of platelet activating factor and nitric oxide, whereas in autoimmune disease it acts by stimulating other cells to produce cytokines or enzymes that then act on the target tissue." The article describes a group of diseases that are mediated by IL-1, including sepsis syndrome, rheumatoid arthritis, inflammatory bowel disease, acute and myelogenous leukemia, insulin-dependent diabetes mellitus, atherosclerosis and other diseases including transplant rejection, graft versus host disease (GVHD), psoriasis, asthma, osteoporosis, periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds inhibit cellular signaling through the IL-1 Type I receptor and are IL-1 antagonists, the inventive compounds are useful for treating all of the above-mentioned diseases.

Detailed Description Text (61):
The compounds of the invention provide a mechanism to maintain homeostasis in cells contacted by primary stimuli through mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of the primary stimulus. For example, administration of the inventive compounds in vivo or ex vivo provide a method to modify cellular behavior which method comprises contacting cells (in vivo or ex vivo) whose behavior is to be modified with an effective amount of an inventive compound or a pharmaceutical composition thereof wherein said method is: (I) a method to inhibit proliferation of tumor cells and said amount is sufficient to inhibit said proliferation; or (2) a method to promote differentiation of hematopoietic stem cells into red blood cells, platelets, lymphocytes, and granulocytes, and said amount is sufficient to promote said proliferation; or (3) a method to suppress activation of T-cells by antigen or IL-2 stimulation, and said amount is sufficient to promote said activation; or (4) a method to suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation and said amount is sufficient to suppress said activation; or (5) a method to enhance the resistance of mesenchymal cells to the cytotoxic effect of tumor necrosis factor and said amount is sufficient to enhance said resistance; or (6) a method to suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand and said amount is sufficient to suppress said antibody production; or (7) a method to inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation and said amount is sufficient to inhibit said proliferation; or (8) a method to lower systemic vascular resistance conferred by endothelial cells and said amount is sufficient to reduce the release of hypertension-inducing substances; or (9) a method to lower systemic vascular resistance induced by endothelial cells and said amount is sufficient to enhance the release of anti-hypertensive substances; or (10) a method to lower expression of adhesion molecules induced by enhancers thereof, and said amount is sufficient to lower said expression; or (11) a method to suppress the activation of T-cells by HIV and said amount is sufficient to suppress said activation thus inhibiting viral replication; or (12) a method to inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or mip-1.alpha. and/or PDGF and/or FGF and said amount is sufficient to inhibit said proliferation; or (13) a method to enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B and said amount is sufficient to enhance said resistance; or (14)

a method to prevent the suppression of growth stimulatory factor production in TNF-treated bone marrow stromal cells and said amount is sufficient to prevent said suppression; or (15) a method to prevent the release of mip-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; or (16) a method to prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; or (17) a method to prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells and said amount is sufficient to prevent said down-regulation; or (18) a method to suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells and said amount is sufficient to enhance said production; or (19) a method to enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation and said amount is sufficient to enhance said resistance; or (20) a method to enhance the antitumor effect of a non-alkylating antitumor agent and said amount is sufficient to enhance said effect, or (21) a method to inhibit the production of osteoclast activating factor in response to IL-1, and said amount is sufficient to inhibit said production, or (22) a method to inhibit degranulation in response to IgE, and said amount is sufficient to inhibit said degranulation, or (23) a method to enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, and said amount is sufficient to enhance said release, or (24) a method to modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, and said amount is sufficient to modulate such slow currents.

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L4: Entry 158 of 158 File: USPT Nov 28, 1995

DOCUMENT-IDENTIFIER: US 5470878 A
TITLE: Cell signaling inhibitors

Detailed Description Text (33):
The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as IL-1 antagonists. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. (1993) 106:328) described the role of IL-1 as "an important rapid and direct determinant of disease." "In septic shock, for example, IL-1 acts directly on the blood vessels to induce vasodilatation through the rapid production of platelet activating factor and nitric oxide, whereas in autoimmune disease it acts by stimulating other cells to produce cytokines or enzymes that then act on the target tissue." The article describes a group of diseases that are mediated by IL-1, including sepsis syndrome, rheumatoid arthritis, inflammatory bowel disease, acute and myelogenous leukemia, insulin-dependent diabetes mellitus, atherosclerosis and other diseases including transplant rejection, graft versus host disease (GVHD), psoriasis, asthma, osteoporosis, periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds inhibit cellular signaling through the IL-1 Type I receptor and are IL-1 antagonists, the inventive compounds are useful for treating all of the above-mentioned diseases.

Detailed Description Text (45):
The inventive compounds provide a method for maintaining homeostasis in cells contacted by primary stimuli by mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of a primary stimulus. For example, administration of an inventive compound in vivo or ex vivo provides a method to modify cellular behavior, the method comprising contacting cells (in vivo or ex vivo), whose behavior is to be modified, with an effective amount of an inventive compound or a pharmaceutical composition thereof wherein said method is a method to: (1) inhibit proliferation of tumor cells and said amount is sufficient to inhibit said proliferation; (2) suppress activation of T-cells by antigen or IL-2 stimulation, and said amount is sufficient to promote said activation; (3) suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation and said amount is sufficient to suppress said activation; (4) suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand and said amount is sufficient to suppress said antibody production; (5) inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation and said amount is sufficient to inhibit said proliferation; (6) lower systemic vascular resistance conferred by endothelial cells and said amount is sufficient to reduce the release of hypertension-inducing substances; (7) lower systemic vascular resistance induced by endothelial cells and said amount is sufficient to enhance the release of anti-hypertensive substances; (8) lower expression of adhesion molecules induced by enhancers thereof, and said amount is sufficient to lower said expression; (9) suppress the activation of T-cells and macrophages by HIV and said amount is sufficient to suppress said activation thus inhibiting viral replication; (10) inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or MIP-1.alpha. and/or PDGF and/or FGF and said amount is sufficient to inhibit said proliferation; (11) enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B and said amount is sufficient to enhance said resistance; (12) prevent the release of MIP-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; (13) prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; (14) prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells and said amount is sufficient to prevent

said down-regulation; (15) suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells and said amount is sufficient to enhance said production; (16) enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation and said amount is sufficient to enhance said resistance; (17) enhance the antitumor effect of a non-alkylating antitumor agent and said amount is sufficient to enhance said effect; (18) to inhibit the production of osteoclast activating factor in response to IL-1, and said amount is sufficient to inhibit said production; (19) inhibit degranulation in response to IgE, and said amount is sufficient to inhibit said degranulation; (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, and said amount is sufficient to enhance said release; (21) modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, and said amount is sufficient to modulate such slow currents; (22) suppress signaling by neurotransmitters including acetyl choline, leuenkephalin and serotonin; or (23) increase seizure theshold.

Detailed Description Text (83):
The inventive compounds provide a method for maintaining homeostasis in cells contacted by primary stimuli by mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of a primary stimulus. For example, administration of an inventive compound in vivo or ex vivo provides a method to modify cellular behavior, the method comprising contacting cells (in vivo or ex vivo), whose behavior is to be modified, with an effective amount of an inventive compound or a pharmaceutical composition thereof. The method is a method to: (1) inhibit proliferation of tumor cells, (2) suppress activation of T-cells by antigen or IL-2 stimulation (3) suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation, (4) suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand, (5) inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation (6) lower systemic vascular resistance conferred by endothelial cells, (7) lower systemic vascular resistance induced by endothelial cells, (8) lower expression of adhesion molecules induced by enhancers thereof, (9) suppress the activation of T-cells and macrophages by HIV, (10) inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or MIP-1.alpha. and/or PDGF and/or FGF, (11) enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B, (12) prevent the release of MIP-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; (13) prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; (14) prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells, (15) suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells, (16) enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation, (17) enhance the antitumor effect of a nonalkylating antitumor agent, (18) to inhibit the production of osteoclast activating factor in response to IL-1, (19) inhibit degranulation in response to IgE, (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, (21) modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, (22) suppress signaling by neurotransmitters including acetyl choline, leuenkephalin and seretonin; or (23) increase seizure theshold.

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L4: Entry 156 of 158 File: USPT Oct 15, 1996

DOCUMENT-IDENTIFIER: US 5565491 A
**** See image for Certificate of Correction ****
TITLE: Use of phosphotyrosine phospatase inhibitors for controlling cellular proliferation

Detailed Description Text (91):
However, phosphotyrosine phosphatase inhibitors can also be used to control proliferation of normal B cells, particularly in situations in which downregulation of the immune response is desired. Such situations include induction of immunosuppression to prevent transplant rejection, as well as in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, and systemic lupus erythematosus, as well as other autoimmune diseases.

Detailed Description Text (103):
Methods according to the present invention can also be used to inhibit phosphotyrosine phosphatases for purposes other than that of treating malignant disease. In particular, phosphotyrosine phosphatase inhibitors can be used to suppress the immune system in order to prevent organ or tissue rejection during transplantation and also in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus, Guillain-Barre Syndrome, and possibly multiple sclerosis.

Detailed Description Text (107):
Methods according to the present invention can further be used to prevent class-switching in antibodies from IgG or IgM to IgE. It is desirable to block IgE production because this type of antibody mediates many allergic responses, particularly immediate-type hypersensitivity reactions such as anaphylaxis, atopy, and urticaria. The CD40 ligand gp39 and the cytokine IL-4act on B cells to induce the switching of the type of antibody produced from IgM to IgE. CD40 and IL-4 mechanisms of action are known to involve tyrosine phosphorylation. Phosphotyrosine phosphatase inhibitors such as BMLOV disrupt the normal pattern of tyrosine phosphorylation, disrupting the class-switching process. The administration of BMLOV, in particular, can markedly inhibit the production of IgE antibody while much less markedly inhibiting the production of IgG subclasses such as IgG1 and IgG4. This leads to the result that the ratio of IgG to IgE increases (Example 14). This result leads to the conclusion that phosphotyrosine phosphatase inhibitors such as BMLOV have value in the treatment of allergy.

Detailed Description Text (140):
BMLOV can inhibit normal tonsillar B cell proliferation driven by stimulation of CD40 via either anti-CD40 antibody or gp39 ligand plus either anti-CD20 antibody or phorbol 12-myristate 13-acetate (PMA). In one experiment, doses of 0.1 to 10 .mu.M had little effect on proliferation (FIG. 3). In a second experiment, a dose of 5 .mu.M gave substantial inhibition of proliferation and a dose of 50 .mu.M completely blocked proliferation (FIG. 4). Variations between the individuals from which the tonsils were derived could account for the differences between these experiments.

Detailed Description Text (141):
Similarly, BMLOV can inhibit the proliferation of normal peripheral B cells. Normal B cell proliferation is mediated in part by the B cell surface molecule CD20, the B cell surface molecule CD40 in conjunction with its ligand gp39, and by the cytokine IL-4. The pharmacologic agent phorbol 12-myristate 13-acetate (PMA) can also be used in combination with these biological stimulation agents to further increase proliferation.

Detailed Description Text (142):

In the experiment reported in Table 4, monoclonal antibodies to CD20 and CD40 were used to stimulate proliferation. Peripheral B cells were isolated from two healthy human volunteers. The cells were stimulated as listed in Table 4 and the effects of various doses of BMLOV on proliferation, as measured by [.sup.3 H] thymidine incorporation, were determined. BMLOV was able to inhibit proliferation induced by CD20, CD40, IL-4 and PMA in the various combinations tested. The cells from donor 2 were more sensitive, indicating some variation among individuals in their sensitivity to the drug.

Detailed Description Text (144):
Standard error did not exceed 8% for donor 1 and 15% for donor 2. Stimulation of CD20 was via monoclonal antibody 1F5 and stimulation of CD40 was via monoclonal antibody G28-5.

Detailed Description Text (182):
The effects of BMLOV were assayed on class-switching in antibody-producing B cells. Human B cells producing antibody were treated with anti-CD40 antibody plus IL-4, which increased production of IgE over 10-fold (Table 7). However, in the presence of 5.6 or 17 .mu.M BMLOV, the increased production of IgE was markedly inhibited. In contrast, the production of IgG1 and IgG4 was much less affected, particularly at a dose of 5.6 .mu.M BMLOV. This selective effect is important because the IgG antibody production is an important response to infectious disease. It would be of value to suppress IgE production for the treatment of allergies while maintaining IgG production, particularly in conditions in which an allergy coexists with an infectious disease. A common example is the exacerbation of allergic rhinitis (hay fever) as the result of a respiratory infection.

Detailed Description Paragraph Table (4):
TABLE 4 INHIBITION OF NORMAL PERIPHERAL B CELL GROWTH BY BMLOV AS MEASURED IN [.sup.3 H]- THYMIDINE INCORPORATION ASSAYS [.sup.3 H]cpm Incorporation For Stimuli: PMA + CD20 + Dose, .mu.m CD40 CD40 PMA + IL4 CD40 + IL4 Donor #1: 0 65587 3574 61941 32499 1 62643 3619 61415 31966 5 58418 3644 48724 33845 10 45330 3422 45278 31637 25 25536 2432 14277 24933 Donor #2: 0 52672 5602 62228 19095 1 49102 4593 53642 16597 5 47624 5681 41892 18824 10 29024 5269 20313 12662 25 15671 856 2730 6013

Detailed Description Paragraph Table (7):
TABLE 7 EFFECT OF BMLOV ON CLASS-SWITCHING IN ANTIBODY-PRODUCING B CELLS Treatment of [Ig], ng/ml: Cells IgG1 Ig64 IgM IgE Untreated 225 0.7 6.6 0.5 Anti-CD40 + IL-4 510 1.7 16.8 5.7 Anti-CD40 + 450 1.7 20.4 3.9 IL-4 + 0.002 .mu.M BMLOV Anti-CD40 + 450 1.1 20.4 2.6 IL-4 + 0.008 .mu.M BMLOV Anti-CD40 + 390 1.3 19.2 4.5 IL-4 + 0.02 .mu.M BMLOV Anti-CD40 + 450 2.7 12.0 5.1 IL-4 + 0.07 .mu.M BMLOV Anti-CD40 + 495 1.2 13.8 7.5 IL-4 + 0.2 .mu.M BMLOV Anti-CD40 + 480 1.3 17.4 5.7 IL-4 + 0.6 .mu.M BMLOV Anti-CD40 + 450 2.7 15.6 3.0 IL-4 + 1.9 .mu.M BMLOV Anti-CD40 + 480 1.8 18.6 1.2 IL-4 + 5.6 .mu.M BMLOV Anti-CD40 + 450 0.8 18.0 0.8 IL-4 + 17 .mu.M BMLOV Anti-CD40 + 60 0.5 5.1 0.2 IL-4 + 50 .mu.M BMLOV

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From: Gambel, Phillip
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To: STIC-ILL
Subject: thyroiditis and oophoritis

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stull, S.J., et la. (1988). Prevention and reversal of experimental autoimmune thyroiditis (EAT) in mice by administration of anti-L3T4 monoclonal antibody at different stages of disease development. Cell. Immunol. 117:188-198.

9/7/31 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07143542 92005735 PMID: 1680568
Suppression in murine experimental autoimmune thyroiditis: in vivo inhibition of CD4+ T cell-mediated resistance by a nondepleting rat CD4 monoclonal antibody.
Nabozny G H; Cobbold S P; Waldmann H; Kong Y C
Department of Immunology and Microbiology, Wayne State University School of Medicine, Detroit, Michigan.
Cellular immunology (UNITED STATES) Nov 1991, 138 (1) p185-96, ISSN 0008-8749 Journal Code: 1246405
Contract/Grant No.: DK 40721; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Genetically susceptible mice become resistant to experimental autoimmune thyroiditis (EAT) induction with mouse thyroglobulin (MTg) and lipopolysaccharide after pretreatment with deaggregated MTg (dMTg). Recent work showed this suppression to be mediated by CD4+ suppressor T cells (Ts). To study Ts action in vivo, we used a rat IgG2a monoclonal antibody (mAb), YTS 177.9, which modulates CD4 antigen in vivo without depleting CD4+ cells. Initial studies showed that after two 1-mg doses of mAb 7 days apart, extensive CD4 antigen modulation of peripheral blood leukocytes occurred within 4 days. Mice given CD4 mAb 24 hr before dMTg (2 doses, 7 days apart) were resistant to EAT induction when immunized with MTg and LPS 20 days later. Also, anti-rat IgG2a titers were reduced following challenge with heat-aggregated rat IgG2a compared to controls. Subsequent analysis of serum in CD4 mAb-treated animals revealed that mAb was present in the circulation for 14 days. Moreover, mice given CD4 mAb and dMTg, then challenged after only 10 days, when CD4 mAb was still circulating, developed a significantly higher incidence of thyroid damage than controls. These findings suggest that modulation of CD4 antigen does not interfere with Ts activation, but the presence of CD4 mAb, at the time of autoantigenic challenge, can interfere with tolerance to EAT induction. Thus, the direct relationship between the presence of CD4 mAb and inhibition of EAT suppression implicates a role for CD4 molecules in the mediation of suppression.
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Subject: oophooritis

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1) griggs et al. j. exp. med., 183 : 801 - 810 (1996)

2) smith et al. j. immunol. 147: 2928 - 2933 (1991)

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From: Gambel, Phillip
Sent: Tuesday, October 14, 2003 5:18 PM
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1) griggs et al. j. exp. med., 183 : 801 - 810 (1996)

2) smith et al. j. immunol. 147: 2928 - 2933 (1991)

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9/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09037705 BIOSIS NO.: 199497046075
Adhesion molecule monoclonal antibodies inhibit experimental autoimmune thyroiditis.
AUTHOR: Metcalfe R A; Tandon N; Tamatani T; Miyasaka M; Weetman A P(a)
AUTHOR ADDRESS: (a)Dep. Med., Univ. Sheffield, Clinical Sci. Centre, Northern General Hosp., Sheffield, S5 7AU**UK
JOURNAL: Immunology 80 (3):p493-497 1993
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To examine the role played by adhesion molecules in thyroid autoimmunity, we have assessed the effect of administering monoclonal antibodies (mAb) against intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) in experimental autoimmune thyroiditis, induced by immunizing rats with thyroglobulin in complete Freund's adjuvant. The antibody against LFA-1, but not against ICAM-1, reduced thyroglobulin antibody production (P lt 0.01) and both antibodies caused a significant reduction (P lt 0.002) in the severity of the thyroidal lymphocytic infiltration. In vitro, both mAb impaired the proliferative response of splenic and lymph node T cells to thyroglobulin, but only the antibody against LFA-1 reduced thyroid cell killing assessed using splenic lymphocytes as effectors. Monoclonal antibodies against both these adhesion molecules appear to inhibit cell-mediated autoimmunity in vivo, but only the LFA-1 mAb reduced the autoantibody response.

11/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05833778 88187613 PMID: 2965739
Thymus and autoimmunity. Transplantation of the thymus from cyclosporin A-treated mice causes organ-specific autoimmune disease in athymic nude mice.
Sakaguchi S; Sakaguchi N
Department of Biophysics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
Journal of experimental medicine (UNITED STATES) Apr 1,1988, 167 (4) p1479-85, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Organ-specific autoimmune diseases such as gastritis, oophoritis, thyroiditis, or insulitis developed in athymic nu/nu mice after engraftment of the thymus from euthymic nu/+ mice treated with cyclosporin A (CsA), a potent immuno-suppressant. The development of autoimmune disease in the nu/nu mice was prevented by inoculation of thymocyte suspensions prepared from normal nu/+ mice, but not by thymocyte suspensions from CsA-treated nu/+ mice. Cotransplantation of normal nu/+ mouse thymus with CsA-treated thymus also suppressed the development of autoimmune disease. Inoculation of spleen cell suspensions prepared from normal adult nu/+ mice prevented autoimmune disease, but inoculation of those from newborn nu/+ mice did not. Thus, CsA appears to interfere selectively with the thymic production of certain suppressor T cells controlling self-reactive (autoimmune) T cells, allowing the latter to expand and cause autoimmune disease.

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9/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09037705 BIOSIS NO.: 199497046075
Adhesion molecule monoclonal antibodies inhibit experimental autoimmune thyroiditis.
AUTHOR: Metcalfe R A; Tandon N; Tamatani T; Miyasaka M; Weetman A P(a)
AUTHOR ADDRESS: (a)Dep. Med., Univ. Sheffield, Clinical Sci. Centre, Northern General Hosp., Sheffield, S5 7AU**UK
JOURNAL: Immunology 80 (3):p493-497 1993
ISSN: 0019-2805
DOCUMENT TYPE: Article
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LANGUAGE: English

ABSTRACT: To examine the role played by adhesion molecules in thyroid autoimmunity, we have assessed the effect of administering monoclonal antibodies (mAb) against intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) in experimental autoimmune thyroiditis, induced by immunizing rats with thyroglobulin in complete Freund's adjuvant. The antibody against LFA-1, but not against ICAM-1, reduced thyroglobulin antibody production (P lt 0.01) and both antibodies caused a significant reduction (P lt 0.002) in the severity of the thyroidal lymphocytic infiltration. In vitro, both mAb impaired the proliferative response of splenic and lymph node T cells to thyroglobulin, but only the antibody against LFA-1 reduced thyroid cell killing assessed using splenic lymphocytes as effectors. Monoclonal antibodies against both these adhesion molecules appear to inhibit cell-mediated autoimmunity in vivo, but only the LFA-1 mAb reduced the autoantibody response.

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11/7/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05833778 88187613 PMID: 2965739
Thymus and autoimmunity. Transplantation of the thymus from cyclosporin A-treated mice causes organ-specific autoimmune disease in athymic nude mice.
Sakaguchi S; Sakaguchi N
Department of Biophysics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205.
Journal of experimental medicine (UNITED STATES) Apr 1 1988, 167 (4) p1479-85, ISSN 0022-1007 Journal Code: 2985109R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Organ-specific autoimmune diseases such as gastritis, oophoritis, thyroiditis, or insulitis developed in athymic nu/nu mice after engraftment of the thymus from euthymic nu/+ mice treated with cyclosporin A (CsA), a potent immuno-suppressant. The development of autoimmune disease in the nu/nu mice was prevented by inoculation of thymocyte suspensions prepared from normal nu/+ mice, but not by thymocyte suspensions from CsA-treated nu/+ mice. Cotransplantation of normal nu/+ mouse thymus with CsA-treated thymus also suppressed the development of autoimmune disease. Inoculation of spleen cell suspensions prepared from normal adult nu/+ mice prevented autoimmune disease, but inoculation of those from newborn nu/+ mice did not. Thus, CsA appears to interfere selectively with the thymic production of certain suppressor T cells controlling self-reactive (autoimmune) T cells, allowing the latter to expand and cause autoimmune disease.

2/7/5 (Item 5 from file: 5)
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06185080 BIOSIS NO.: 000086019262
THYMUS AND AUTOIMMUNITY TRANSPLANTATION OF THE THYMUS FROM CYCLOSPORIN A-TREATED MICE CAUSES ORGAN-SPECIFIC AUTOIMMUNE DISEASE IN ATHYMIC NUDE MICE
AUTHOR: SAKAGUCHI S; SAKAGUCHI N
AUTHOR ADDRESS: DIV. IMMUNOL., DEP. MED., STANFORD UNIV. SCH. MED., STANFORD, CALIF. 94305.
JOURNAL: J EXP MED 167 (4). 1988. 1479-1485. 1988
FULL JOURNAL NAME: Journal of Experimental Medicine
CODEN: JEMEA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Organ-specific autoimmune diseases such as gastritis, oophoritis, thyroiditis, or insulitis developed in athymic nu/nu mice after engraftment of the thymus from euthymic nu/ + mice treated with cyclosporin A (CsA), a potent immunosuppressant. The development of autoimmune disease in the nu/nu mice was prevented by inoculation of thymocyte suspensions prepared from normal nu/ + mice, but not by thymocyte suspension from CsA-treated nu/ + mice. Cotransplantation of normal nu/ + mouse thymus with CsA-treated thymus also suppressed the development of autoimmune disease. Inoculation of spleen cell suspensions prepared from normal adult nu/ + mice prevented autoimmune disease, but inoculation of those from newborn nu/ + mice did not. Thus, CsA appears to interfere selectively with the thymic production of certain suppressor T cells controlling self-reactive (autoimmune) T cells, allowing the latter to expand and cause autoimmune disease.

2/7/1 (Item 1 from file: 5)
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09969068 BIOSIS NO.: 199598423986
Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25): Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases.
AUTHOR: Sakaguchi Shimon(a); Sakaguchi Noriko; Asano Masano; Itoh Misako; Toda Masaaki
AUTHOR ADDRESS: (a)Dep. Immunopathol., Tokyo Metropolitan Inst. Gerontol., 35-2 Sakaecho, Itabashi-ku, Tokyo 173**Japan
JOURNAL: Journal of Immunology 155 (3):p1151-1164 1995
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Approximately 10% of peripheral CD4+ cells and less than 1% of CD8+ cells in normal unimmunized adult mice express the IL-2 receptor alpha-chain (CD25) molecules. When CD4+ cell suspensions prepared from BALB/c nu/+ mice lymph nodes and spleens were depleted of CD25+ cells by specific mAb and C, and then inoculated into BALB/c athymic nude (nu/nu) mice, all recipients spontaneously developed histologically and serologically evident autoimmune diseases (such as thyroiditis, gastritis, insulitis, sialoadenitis, adrenalitis, oophoritis, glomerulonephritis, and polyarthritis); some mice also developed graft-vs-host-like wasting disease. Reconstitution of CD4+CD25+ cells within a limited period after transfer of CD4+CD25+ cells prevented these autoimmune developments in a dose-dependent fashion, whereas the reconstitution several days later, or inoculation of an equivalent dose of CD8+ cells, was far less efficient for the prevention. When nu/nu mice were transplanted with allogeneic skins or immunized with xenogeneic proteins at the time of CD25- cell inoculation, they showed significantly heightened immune responses to the skins or proteins, and reconstitution of CD4+CD25+ cells normalized the responses. Taken together, these

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08[illegible]6002 BIOSIS NO.: 000093070925
AUTOIMMUNE DISEASE OF THE OVARY INDUCED BY A ZP3 PEPTIDE FROM THE MOUSE ZONE PELLUCIDA
AUTHOR: RHIM S H; MILLAR S E; ROBEY F; LUO A-M; LOU Y-H; YULE T; ALLEN P; DEAN J; TUNG K S K
AUTHOR ADDRESS: DEP. PATHOL., UNIV. VA., CHARLOTTESVILLE, VA. 22908.
JOURNAL: J CLIN INVEST 89 (1). 1992. 28-35. 1992
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We describe a novel experimental system in mice for the study of ovarian autoimmune disease, a condition encountered in women with premature ovarian failure. The ovarian autoimmune disease is induced in B6AF1 mice by a 15-amino acid peptide (Cys-Ser-Asn-Ser-Ser-Ser-Ser-Gln-Phe-Gln-Ile-His-Gly-Pro-Arg) from mouse ZP3, the sperm-binding component of the zona pellucida that surrounds growing and mature oocytes. Whereas the peptide induces both T cell and antibody responses, adoptive transfer of CD4+ T cell lines derived from affected animals causes oophoritis without observable antibodies to the zona pellucida peptide. The primacy of the T cell response in the pathogenesis of disease is further substantiated by defining oophoritogenic peptides as small as eight amino acids (Asn-Ser-Ser-Ser-Ser-Gln-Phe-Gln) that do not elicit an antibody response to the full-length ZP3 peptide. The identification of a well characterized peptide as a causative agent of autoimmune oophoritis should facilitate understanding of the pathogenesis of this T cell-mediated autoimmune disease. Because the proteins of the zona pellucida are conserved among mammals (the mouse and human ZP3 proteins are 67% identical), this murine model may lead to better understanding of the pathogenesis of human autoimmune oophoritis.

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1644 8/30

2/7/12 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

03075364 EMBASE No: 1986232941
Lymphocyte dysfunction in autoimmune oophoritis. Resumption of menses with corticosteroids
Rabinowe S.L.; Berger M.J.; Welch W.R.; Dluhy R.G.
Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115 United States
American Journal of Medicine (AM. J. MED.) (United States) 1986, 81/2 (347-350)
CODEN: AJMEA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

In a 32-year-old woman with secondary amenorrhea and biopsy-proven oophoritis, the circulating T lymphocytes were examined utilizing monoclonal antibody L243 to the nonpolymorphic region of the Ia antigen. The percentage of peripheral T cells expressing the Ia 'immune-associated' antigen was 5.6 percent (normal 3 percent or less). With corticosteroid therapy, the percentage decreased to 2 percent and menses resumed after secondary amenorrhea or two years' duration. Following cessation of steroid administration, the percentage of Ia-positive T cells rose to 7.0 percent and secondary amenorrhea redeveloped in the patient. After corticosteroid therapy was reinstituted, menses resumed and the percentage of Ia-positive T cells fell to normal. This report represents additional new evidence of immune dysfunction in patients with 'autoimmune' oophoritis.

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From: Gambel, Phillip
Sent: Tuesday, October 14, 2003 3:47 PM
To: STIC-ILL
Subject: oophoritis

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2/7/11 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

05028929 EMBASE No: 1992169145
Causes and mechanism of autoimmune disease: Cyclosporin A as a probe for the investigation
Sakaguchi N.; Sakaguchi S.
Department of Patology 0612, University of California, School of Medicine, 9500 Gilman Drive,La Jolla, CA 92093-0612 United States
Journal of Investigative Dermatology (J. INVEST. DERMATOL.) (United States) 1992, 98/6 SUPPL. (70S-76S)
CODEN: JIDEA ISSN: 0022-202X
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Organ-specific autoimmune disease can be elicited in rodents by manipulating the thymus/T cells. For example, elimination of a particular T-cell subset causes organ-specific autoimmune diseases, such as thyroiditis and gastritis, in otherwise normal mice. Environmental agents can cause similar autoimmune diseases by affecting the thymus/T cells. Cyclosporin A (CsA), a potent immunosuppressive drug, is an example. When a particular strain of newborn mice are daily administered with CsA for a limited period, they spontaneously develop organ-specific autoimmune disease, such as gastritis with anti-parietal cell autoantibodies, later in life. CsA abrogates the production of CD4sup + T cells and CD8sup + T cells in the thymus. Consequently, these T cells are substantially depleted from the peripheral lymphoid organs, especially when the drug is administered from the day of birth. The autoimmune disease is prevented when CsA-treated newborn mice as inoculated with splenic T cells from normal syngeneic adult mice. On the other hand, removal of the thymus immediately after neonatal CsA treatment produces autoimmune disease with a higher incidence and in a wider spectrum of organs, i.e., thyroiditis, sialoadenitis of the salivary gland, gastritis, insulitis of the endocrine pancreas, adrenalitis, oophoritis, or orchitis. Each autoimmune disease is accompanied by the development of circulating autoantibodies specific for the corresponding organ-specific antigens. These findings taken together indicate that CsA ccauses autoimmune disease not by affecting the target self-antigens, but by interfering with a thymus/T cell-dependent control mechanism on the production/expansion of pathogenic self-reactive T cells. Various other environmental insults (such as ionizing radiation or virus) can also cause similar autoimmune diseases, presumably by a similar mechanism.